UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/630,578	07/30/2003	Carl P. Schaffner	4892-102 US	8654

7590 05/24/2004

Patrick H. Higgins
Mathews, Collins, Shepherd & McKay
Suite 306
100 Thanet Circle
Princeton, NJ 08540

EXAMINER	
HENLEY III, RAYMOND J	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 05/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/630,578	SCHAFFNER ET AL.	
	Examiner	Art Unit	
	Raymond J Henley III	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-29 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-29 is/are rejected.

7)☐ Claim(s) ____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

CLAIMS 1-29 ARE PRESENTED FOR EXAMINATION

Specification

The disclosure is objected to because of the following informality:

In order to perfect applicants' priority claim, the specification at page 1, first line should be amended to read ---This application claims priority to U.S. Provisional Application 60/399,690.----.

Appropriate correction is required.

Claim Objections

Claims 2-10, 12-17 and 19-29 are objected to because of the following informalities:

In claims 2-10, 12-17, 19-24 and 26-29, the first term should be change from "A" to ---The---.

In claims 13-17 and 20-24, the presence of the parentheses renders the claim grammatically incorrect.

In claim 25, line 2, "azetidinone20" should read as ---azetidinone---. Appropriate correction is required.

Claim Rejection - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment a cholesterol-associated tumor, does not reasonably

provide enablement for the prevention of a cholesterol-associated tumor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The burden of enabling the prevention of a cholesterol-associated tumor would be much greater than that of enabling the treatment of such conditions. In the instant case, the specification does not provide guidance as to how one skilled in the art would accomplish the objective of preventing of such conditions or how a patient could be kept from ever being susceptible to these conditions. Nor is there any guidance provided as to a specific protocol to be utilized in order to show the efficacy of the presently claimed active ingredients for preventing a cholesterol-associated tumor.

Specifically, it is highly unlikely, and the Office would require experimental evidence to support the contention that the claim specified actives could actually prevent a cholesterol-associated tumor by simply administering, by any method, an amount of the claim specified active agents. The specification fails to enable one of ordinary skill in the art to practice and use the compositions/article of manufacture in the present claim for preventing the above conditions.

The term "prevention" or "preventing" is synonymous with the term "curing" and both circumscribe methods of treatment having absolute success. Since absolute success is not reasonably possible with most diseases/disorders, especially those having etiologies and pathophysiological manifestations as complex/poorly understood as cholesterol-associated tumors, the specification is viewed as lacking an adequate written description of the same.

That, in fact, the etiologies of cholesterol-associated tumors are complex/poorly understood, the Examiner points to the present specification at page 1, lines 18-28 where

applicants have set forth:

> "Although cholesterol metabolism has been studied extensively in the liver and intestinal tract of humans and experimental animals little attention has been directed to the cholesterol metabolism in the male prostate gland and the female mammary gland in both their normal and pathologic diseased states. ***The etiology and progression for benign and malignant tumors of these glands still remains largely a mystery.*** Cholesterol-rich diets have had a significant epidemiological association with the variety of human cancer diseases. Particularly, cancers of the prostate and mammary glands and of the colon have been linked to high-fat "western" diets including the intake of fat of animal origin. Kolonel, et al., 1999, J. Natl. Cancer Inst., 91:414-428; Willett, 1989, Nature, 338:389-394. ***The mechanisms, however, by which these cancers are initiated and progress, as related to the dietary fat, are poorly understood.***" (emphasis added)

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the appropriate factors from those above are applied to the present application (see below) and weighed, it is the examiner's position that the present specification would only enable the skilled artisan to treat a cholesterol-associated tumor.

(1) The nature of the invention/state of the prior art, relative skill of those in the art, the predictability in the art.

The claims are directed to methods, compositions and articles of manufacture useful for treating or preventing cholesterol-associated tumors. The relative skill of those in the art is high.

(2) The breadth of the claims

The claims are limited to cholesterol-associated tumors and inclusive of methods,

compositions and articles of manufacture useful for the prevention of the above conditions and the mere administration of the claimed actives for treating or preventing such tumors.

(3) The amount of direction or guidance presented and presence or absence of working examples.

The specification provides merely provides statements that cholesterol-associated tumors may be prevented. No experimental data is present that shows, in fact, the prevention of a cholesterol-associated tumor.

(4) The quantity of experimentation necessary.

Applicants have failed to provide guidance and information sufficient to allow the skilled artisan to ascertain how to absolutely cure, i.e., prevent, cholesterol-associated tumors. Testing would be necessary on each form of administration and on each form of cholesterol-associated tumor with no expectation that such conditions could successfully be prevented, as claimed instantly.

Given the above, it is deemed that the present claims are broader than enabled by the present specification and thus are properly rejected.

Claim Rejection - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 4-6, 14-17, 21-24 and 29 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The expression "consisting essentially of" renders the claimed subject matter indefinite. The expression is employed to set forth the members of a Markush group of elements. Such a group must be definite as to the members included therein. The use of the expression "consisting essentially of", however, opens the group for inclusion of other, but non-specified, members. Thus, the metes and bounds of the subject matter for which applicants are seeking patent protection are unclear.

Claim Rejection - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-14, 16-21 and 23-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Applicants' acknowledgments at page 1, line 29 – page 2, line 18 of the specification and in view of Dugar et al. (WO 94/17038), Roenblum et al. (WO 95/08532) Burnett et al. (WO 93/02048) and Waldstreicher et al. (U.S. Patent Application Publication 2001/0041713).

At page 1, line 29 – page 2, line 18 of the specification, applicants acknowledge "The polyene macrolides and in particular, the aromatic heptaene macrolide, candicidin, have been in clinical use for the treatment of human benign prostatic hyperplasia for many years in several countries. Various other hypocholesterolemic drugs that interfere with cholesterol absorption and resorption in the gastrointestinal tract have also been in clinical use for the same human prostatic disease. Schafler, 1983, in: "Benign Prostatic Hypertrophy", Frnnk Hinman, Jr. ed. Springer-velag, New York, pp.280-307 reviewed clinical studies with candicidin and other polyene macrolides. Candicidin in long-term rat studies has been shown to inhibit tumor initiation and progression as compared to untreated controls. Haditirto, 1974, PII.D. Dissertation, Rutgers University. Other inhibitors of cholesterol absorption - resorption include the bile acid sequestering anionic exchange resins such as Cholestyramine® and Colestipol®.

These have also been shown to alter the course of prostatic disease in animals and humans. Colestipol® inhibited benign prostatic hypertrophy in hamsters. Wang. et al., 1976, lnvestigative Urol. 14:66-71. Cholestyramine® has been shown to be effective in some patients with prostatic carcinoma. Addleman, 1972, N. England J. Med., 287:1047. As hypocholesterolemic drugs, the phytosterols, beta-sitosterol and stigmasterol, for example, are also known for their ability to inhibit cholesterol absorption and resorption by a mass action effect requiring large doses. ln a controlled double blind study beta-sitosterol was found to be effective in the treatment of benign prostatic hyperplasia. Ebbinghaus et al., 1977, Z. A11M.Med., 53:1054-1058. It has been approved for human use in Europe."

The differences between the above and the claimed subject matter lies in that the above fails to teach:

(1) the use of the presently claimed azetidinone-based cholesterol absorption inhibitors for the same purposes as the above mentioned cholesterol absorption inhibitors as well as articles of manufacture;

(2) a combination of the presently claimed azetidinone-based cholesterol absorption inhibitors with the presently claimed conventional anti-cancer agents (claims 11-29) ; and

(3) the claimed dosage amounts and articles of manufacture.

However, to the skilled artisan, the claimed subject matter would have been obvious because:

(1) Dugas, Roenblum et al. and Burnett et al. teach the claimed azetidinone compounds as known cholesterol absorption inhibitors (see Dugas at the abstract, page 6, lines 30-31 and page 27, Example 37; Rosenblum at the abstract, page 5, lines 8-9 and page 32, Example 6; and Burnett et al. at the abstract, page 6, line 17 and page 27, lines 2-5). The skilled artisan would have been motivated to employ them for the cholesterol absorption inhibitors as acknowledged by applicants because the artisan would have had at least a reasonable expectation, based on their similar mechanism of action, that they too could be used to treat both benign and malignant prostate tumors.

(2) Waldstreicher et al. teaches the use of finasteride, bicalutamide, flutamide, pilutamide, leuprolide acetate, goserelin acetate, paclitaxel and docetaxel for the treatment of prostate cancer (see page 1, col. 2, section [0013], line 7 and page 2, the continuation of section [0018] at various lines therein). It has been held that it is considered prima facie obvious to have combined two or more ingredients each of which was known to be useful for the same purpose in order to form a third composition that is useful for the very same purpose. The idea for combining them flows logically from their have been used separately. See In re Kerkhoven 205

U.S.P.Q. 1069 (CCPA 1980) and the cases cited therein. The skilled artisan would have been motivated to combine such ingredients in order to achieve at least additive results and to provide the individual being treated with the most convenient, effective therapy possible.

(3) Daily dosages for the azetidinone-based cholesterol lowering agents are taught to be from about 7 to 30 mg/kg of body weight per day by Dugar et al. (page 13, line 27); from about 0.1 to 30 mg/kg of body weight per day by Rosenblum et al. (page 23, line 21); and from about 7 to 30 mg/kg of body weight per day by Burnett et al. (page 29, line 9). The determination of the optimum dosage amount to employ would have been a matter well within the purview of the skilled artisan and the artisan would have been motivated to do so in order to provide the most effective therapy possible. Also, the selection of a particular packaging arrangement, such as the claimed article of manufacture, would have been a matter well within the purview of the skilled artisan as such articles are commonly used in the pharmaceutical art to facilitate both the manufacture and distribution of active agents.

Claims 15 and 22 are not subject to the above rejection because the prior art fails to teach or suggest the treatment of a cholesterol-associated tumor or a composition in which the presently claimed azetidinone-based cholesterol lowering agents are utilized in combination with the selective estrogen receptor modulators to which claims 15 and 22 are limited.

None of the claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Raymond J Henley III whose telephone number is 571-272-0575. The examiner can normally be reached on M-F, 8:30 am to 4:00 pm Eastern Time.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel can be reached on 571-272-0584. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Raymond J Henley III
Primary Examiner
Art Unit 1614

May 19, 2004